UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

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MEMORANDUM

FROM: Kathryn Boyle, CoChair IIFG

and

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TO: Robert Forrest, Chief
Minor Use, Inerts, and Emergency Response Branch

SUBJECT: IIFG Decision Documents on Reassessing Exemptions from the Requirement of a Tolerance for the Mineral Acids (Hydrochloric, Carbonic, Phosphoric, and Sulfuric) and their Ammonium, Calcium, Ferrous, Ferric, Magnesium, Potassium, Sodium, and/or Zinc Salts

Collectively these Decision Documents cover four mineral acids and the salts of these acids. The individual Decision Documents are: (1) Hydrochloric Acid and Salts, (2) Salts of Carbonic Acid, (3) Phosphoric Acid and Salts, and (4) Sulfuric Acid and Salts. The Inert Ingredient Focus Group reassessment is based on various conclusions of the FAO/WHO Joint Expert Committee on Food Additives, conclusions of various FDA GRAS (Generally Recognized As Safe) Assessments, information previously used by OPP as part of the reregistration process, and other information available on government websites.

In total 46 exemptions from the requirement of a tolerance in 40 CFR 180 are reassessed. This total consists of 18 in the phosphoric acid document, nine in the hydrochloric acid document, six in the carbonic acid document, and 13 in the sulfuric acid document.

INERT INGREDIENT FOCUS GROUP

DECISION DOCUMENT for

Sulfuric Acid and Salts

Petition No.: no

Tolerance Reassessments?: yes

Chemical Category/Group: mineral acid and salts

The following describes the various ways that sulfuric acid and its salts are used.

Table 1: Use Pattern (pesticidal - inert ingredient)

Chemical Name	Inert PC Code	40 CFR 180.1001	Inert Use Pattern (Pesticidal)	Current Inert List
sulfuric acid	878001	(c)	0.1% of pesticide formulation; pH control agent	3
ammonium sulfate	805601	(c)	solid diluent, carrier	4B
ferric sulfate	900332	(c)	solid diluent, carrier	4B
magnesium sulfate	850503	(c)	solid diluent, carrier safener	4B
potassium sulfate	805603	(c)	solid diluent, carrier	4B
sodium sulfate	805604	(c), (e)	solid diluent, carrier	4B
sodium bisulfate	873201	(d)	acidifying/buffering agent	4B
zinc sulfate (basic and monohydrate)	889001 911567	(c), (c), (e)	coating agent solid diluent, carrier water repellent, dessicant	3

There is also a tolerance exemption for ferrous sulfate in 40 CFR 180.2.

The tolerance exemption for calcium sulfate (40 CFR 180.1001(e)) was reassessed in the IIFG Decision Document “Weathered Materials”, dated January 31, 2002. It is classified as List

4A.

At this time, only sulfuric acid, ferrous sulfate monohydrate, ferric sulfate, sodium bisulfate, and zinc sulfate are used as active ingredients. There are no longer any EPA-registered active ingredient uses for any of the other above-listed sulfate salts.

Table 2: Use Pattern (pesticidal - active ingredient)

Chemical Name.	**Active PC Code**	**40 CFR**	**Number of Products**	**Active Use Pattern (Pesticidal)**
sulfuric acid	078001	180.1019	8	used to kill bacteria on potatoes, milking equipment and in food processing areas; as a dessicant
ferrous sulfate monohydrate		180.2	15	used to kill moss and algae on ornamentals and turf
ferric sulfate	034902	none	2	used to kill moss on ornamental lawns and turf
sodium bisulfate	073201	none	3	used to kill bacteria on poultry , in toilet bowls, and in air treatment
zinc sulfate monohydrate	527200	none	2	used to kill moss on wood and other surfaces

Table 3: Use Pattern (FDA GRAS):

Chemical	**GRAS Citation**	**GRAS Uses**
sulfuric acid	21 CFR 184.1095	pH control agent, processing aid
ammonium sulfate	21 CFR 184.1143	dough strengthener, firming agent, processing aid
ferrous sulfate	21 CFR 184.1315	nutrient supplements, processing aid, use in infant formula
ferric sulfate	21 CFR 184.1307	flavoring agent
magnesium sulfate	21 CFR 184.1443	flavor enhancer, nutrient supplement, processing aid

potassium sulfate	21 CFR 184.1643	flavoring agent and adjuvant
zinc sulfate	21 CFR 182.8997	(no limitations specified)

Sulfuric acid also has uses in food contact surface sanitizing solutions under 21 CFR 178.1010.

Table 4: Use Pattern (non-pesticidal)

Chemical	Uses
sulfuric acid	used in **fertilizers**, chemicals, dyes and pigments, etchant, alkylation catalyst, electroplating baths, iron and steel, rayon and film, industrial explosives, lab reagent, nonferrous metallurgy
ammonium sulfate	manufacture of ammonia alum; in the manufacture of hydrogen sulfide to free it from nitrogen oxides; analytical uses; freezing mixtures; flameproofing fabrics and paper; manufacture of viscose silk; tanning, galvanizing iron; in fractionation of proteins.
ferric sulfate	preparation of iron alums, other iron salts and pigments; coagulant in water purification and sewage treatment; aluminum etching; pickling stainless steel and copper; as mordant in textile dyeing and calico printing; soil conditioners; polymerization catalyst.
magnesium sulfate	also known as epsom salts; as a cathartic and analgesic in medicine; finishing agent for textiles; as water-correcting agent in brewing industry; component of fireproofing compositions, preservatives, tanning & coagulating agents; chemical intermediate for magnesium trisilicate; component of nickel baths for plating other metals; catalyst support for platinum in sulfuric acid production
potassium sulfate	**fertilizer** for chloride-sensitive crops (tobacco); accelerator in wallboard (construction industry); agent in manufacture of glass; cathartic in human medicine; water-corrective agent for foods (brewery water); setting-expansion control agent for dental materials
sodium sulfate	tanning; pharmaceuticals; freezing mixtures; laboratory reagent
zinc sulfate	zinc sulfate & hydrated lime, 8 lb of each to 100 gal of water, are used to prepare spray called zinc-lime which is the zinc equivalent of bordeaux mixt. Zinc-lime is used extensively for control of bacterial spot disease of peaches. depressant in froth flotation, eg, for lead-zinc ores; component of spinning bath in manufacturer of rayon; chemical intermediate for manufacture of lithopone (pigment), carbamate fungicides (zineb), zinc metal, other zinc compounds (zinc stearate); component of zinc plating baths; chemical for water treatment; component of cosmetics (skin fresheners); reagent for paper bleaching; in manufacter of glue; accelerating agent in dental impression material; agent in textile dyeing and printing; preservative for wood and hides; fireproofing agent

It should be noted that potassium sulfate has use as a fertilizer and sulfuric acid is used in the preparation of fertilizers. Plants need various elements (metals and non-metals) for proper growth. Especially for agricultural crops, plants are supplied these elements as part of chemical fertilizers. The most important elements for plant growth are nitrogen, phosphorus, and potassium. Other metals needed in the soil for plant up-take are calcium, magnesium, iron, and trace elements such as zinc. Potassium sulfate is intentionally added to growing agricultural crops as needed to promote plant growth.

Assessment of Sulfuric Acid and its Salts

Sulfuric acid and its ammonium, sodium, potassium, calcium, magnesium, iron, and zinc salts are being assessed as a group due to their chemical similarities. Due to its acidic nature the toxicity of sulfuric acid will be different from those of the more neutral sulfate salts. However, these sulfate salts all contain the sulfate ion (as either HSO_4^{-1} or SO_4^{-2}), and thus share some common chemistries. A major focus of this assessment is the work previously performed by FDA in assessing the safety of these chemicals as food additives.

1. Physical/Chemical Properties:

The physical and chemical properties of sulfuric acid and its various salts are described in the May 7, 2002 EFED Assessment. See attached.

2. Information Sources:

The following information was used in performing this assessment: The available information consisted of information retrieved from various websites, such as,

- EPA (www.epa.gov),
- NIOSH, (www.cdc.gov/niosh/ipcsneng/neng1197.html), (www.cdc.gov/niosh/ipcsneng/neng0362.html), (www.cdc.gov/niosh/74-128.html) (www.cdc.gov/niosh/idlh/7664939.html)
- TOXNET (www.toxnet.nlm.nih.gov.)
- NTP (ntp-server.niehs.nih.gov/NewHomeRoc/9RoCFacts.html)
- WHO (www.inchem.org/documents/jecfa/jecmono/v05je83.htm) and (www.inchem.org/documents/jecfa/jecmono/40abcj43.htm)

Various FDA GRAS Assessments were used, as well as, the FAO/WHO Assessment for sodium sulfate.

3. NIOSH (National Institute for Occupational Safety and Health)

The NIOSH IDHL (immediately dangerous to life or health) Documentation and the International Chemical Safety Card for sulfuric acid indicate that it is a colorless, oily, odorless liquid. The IDHL is 15 mg/m^3. The TLV (Threshold Limit Value) is 1 mg/m^3 (TWA). Sulfuric acid reacts violently with water. It is corrosive to the skin and the respiratory tract, and on ingestion.

The NIOSH International Chemical Safety Card for magnesium sulfate indicates that a TLV has not been established. No effects were noted.

4. Acid Characteristics

An acid is a substance that when dissolved in water yields H^+ ions. The increase of the concentration of the H^+ ions lowers the pH. Mineral acids contain a non-metal such as phosphorus, nitrogen, sulfur, or chlorine which may or may not be combined with oxygen. When combined with oxygen, these anions can be referred to as oxyanions. Strong acids are those acids that when dissolved completely transfer their H^+ ions to water. Sulfuric acid is an example of a strong acid.

5. Cations: Sodium, Potassium, Calcium, Magnesium, Iron, and Zinc

Generally, a salt of a strong acid, such as sulfuric acid, when dissolved in water, dissociates to yield the sulfate anion (an anion which is negatively charged) and a positively charged cation. In the human body, these salts tend to dissociate and thus, for the most part, react in the body as the anion and the cation.

Metals such as calcium, sodium, magnesium, potassium, iron and zinc are required for proper functioning of human biological systems. For risk assessment purposes an important feature of these metals is that overall the body does have an effective means of processing them. The primary means of exposure to these cations is ingestion. Four of the most common cations required for functioning of human biology are: sodium, potassium, calcium and magnesium. Chemically, sodium and potassium belong to the same chemical family: calcium and magnesium belong to a different chemical family.

Sodium:

The average human body burden of sodium is approximately 20 grams (g) for a 70 kilogram (kg) adult. The sodium cation is necessary for the nerves and muscles to function properly. It is the principal cation of extracellular fluid, and helps to maintain the body’s water balance. These electrolytes, the electrically charged ions in the body fluids, consist to a great extent of sodium and potassium. There is no Recommended Dietary Allowance (RDA) for sodium.

Potassium:

The average human body burden of potassium is approximately 140 g for a 70 kg adult. The potassium cation is important in regulating blood pressure, regulating cellular water content, maintaining proper pH balance, and transmission of nerve impulses. It helps to regulate the electrical activity of the heart and muscles. The potassium RDA is 900 mg/day.

Calcium:

The average human body burden of calcium is approximately 1 kg for a 70 kg adult; or 1/70th of our weight is calcium. The calcium cation is necessary for bone and teeth formation. It is also important to the proper functioning of nerves, enzymes, and muscles, and plays a role in blood clotting and the maintenance of cell membranes. The RDAs for calcium are 1000 mg/day for adults aged 19 to 50 years and 1200 mg/day for individuals older than 50 years.

Magnesium:

The average human body burden of magnesium is approximately 20 g for a 70 kg adult. The magnesium cation is also used in building bones. It plays a role in releasing energy from muscles and regulating body temperature. The RDA for magnesium is 310 to 320 mg/day for adult females and 400 to 420 mg/day for adult males with the RDA increasing with increasing age.

Two common metal cations that are needed for functioning of human biology, but in smaller amounts often referred to as trace, are iron and zinc.

Iron:

The human body burden of iron is approximately 4.1 g for a 70 kg adult. Iron functions as a carrier of oxygen. The hemoglobin molecule in blood transports oxygen from the lungs to the cells. The myoglobin molecule supplies oxygen to muscle cells. Iron deficiency is characterized by anemia, stunted growth, fatigue, and lowered resistance to infection. The RDAs for iron are 10 mg/day [0.14 mg/kg/day for an adult (70 kg) male (25 to 50 years)] and 15 mg/day [0.25 for an adult (60 kg) female (19 to 50 years)]. Pregnant and nursing woman have increased requirements for iron.

Dietary iron is poorly absorbed. The intestinal mucosa is a limiting factor in iron absorption. Normal absorption is about 1 mg/day in an adult male, and about 1.4 mg/day in an adult female. Absorption occurs in the divalent (ferrous) form, which must then be oxidized to the trivalent (ferric) form for use. Acute toxicity of iron ingested from normal dietary sources has not been reported. However, death especially in young children has resulted from ingestion of large overdoses of medicinal iron. (doses ranging from 40 to 1600 mg/kg - average 900 mg/kg). It is noted that the iron from ferric salts is less well absorbed than that from ferrous salts.

Zinc:

The average human body burden of zinc is approximately 100 milligram (mg) for a 70 kg adult. The zinc cation is a component of many enzymes and therefore has substantial involvement in many metabolic processes. It also assists in wound healing, blood formation, and general growth and maintenance of the body's tissues. The RDAs for zinc are 15 mg/day [0.21 mg/kg/day for an adult (70 kg) male] and 12 mg/day [0.2 mg/kg/day for an adult (60 kg) female]. According to FDA, the average daily intake of zinc from food (including water) was 0.23 mg/kg/day in the early 1980s. Consuming too much zinc (i.e. , 10 to 15 times the RDA) can cause health concerns such as anemia, pancreatic and kidney effects, and certain developmental effects. Consuming too little zinc can cause loss of appetite , decreased sense of taste and smell, decreased immune function, slow wound healing, skin sores, and developmental effects.

6. Ammonium Salt:

Ammonium sulfate dissociates to the negative anion and the positively charged ammonium cation (NH_4^+). Humans cannot convert atmospheric nitrogen to any form that can be used as part of any of the various metabolic cycles. Therefore, reduced nitrogen (NH_4^+) has to enter the body from an outside source. These sources are the nitrogen-containing amino acids in protein which are consumed daily as part of the diet. Although the human body can produce some amino acids, ten amino acids are considered "essential" amino acids, i.e., they must be consumed in the diet.

Generally the body works to maintain a balance of nitrogen intake and nitrogen excretion. The estimated daily ammonia intake through food and drinking water is 18 mg. In contrast, 4000 mg of ammonia per day are produced endogenously in the human intestine.

Ammonia and the ammonium ion are integral components of normal human metabolic processes. Ammonia is released following deamination that occurs when protein is used by the body for energy production. The liver converts ammonia via the urea cycle into urea. According to FDA in the "Evaluation of the Health Aspects of Certain Ammonium Salts as Food Ingredients" (1974), "the normal liver so readily detoxifies ammonium ion from alimentary sources that blood concentrations of ammonium salts do not rise to the levels necessary to evoke toxic response." Approximately 80% of the body's excess nitrogen is eliminated through the kidneys as urea, approximately 25 to 30 grams per day.

7. Toxicological Profile Table

The Agency has not reviewed any of the toxicological studies in the following table for sulfuric acid or any of its salts. The reviews of these studies were obtained from Toxnet, as well as other government websites.

Table 5: Toxicological Profile

Chemical	Toxicity	Other Information
Sulfuric Acid	Solutions of greater than 10% are severely corrosive by all routes of exposure; Solutions of less than >10% are strong irritants; IARC: There is sufficient evidence that occupational exposure to strong-inorganic-acid mists containing sulfuric acid is carcinogenic; ATSDR: No significant developmental or reproductive effects in mice or rabbits exposed to 20 mg/m^3 sulfuric acid aerosols 7 hours per day on gestation days 6 to 15	CERCLA Reportable Quantity: greater than 1000 lb (454 kg); 1993 US production= 80.3 billion lbs;
Ammonium Sulfate	13 week oral in rats; doses 0, 0.38, 0.75, 1.5, 3.0%; NOEL = 1.5% in males (886 mg/kg/day), 3% in females (1975 mg/kg/day), (HDT)	
Ferric Sulfate	Irritant to skin, eyes and mucous membranes; Excessive iron intake may cause toxicity	Primary use is in waste water treatment;

Magnesium Sulfate	Cathartic; Massive doses may cause systemic toxicity primarily loss of fluid and electrolytes; Negative in Ames TA100, TA1535, TA98 with and without activation; Negative in *E.coli* with and without activiation; Lowest published oral toxic dose in humans: 428 mg/kg (m) 351 mg/kg(f); Changes in serum composition (f,m), muscle weakness (f,m), cardiac arrhythmias (f); Lowest published lethal dose in rats after oral exposure 5g/kg	US production $5.7x10^{11}$g (1985)
Potassium Sulfate	Saline cathartic; Systemic toxicity unlikely unless massive doses consumed; Toxicity results from excessive loss of fluid and electrolytes.	1985 US production $2x10^{11}$g; EPA Drinking Water standard: 250,000 ug/L sulfate ion
Sodium Sulfate	Mouse oral LD_{50} = 5989mg/kg; Non-toxic and non-irritating to skin and mucous membranes; Saline cathartic; systemic toxicity unlikely unless massive doses consumed; Toxicity results from excessive loss of fluid and electrolytes; Negative in cell transformation (viral enhanced) in Syrian hamster embryo (SA7/SHE) cells; Positive in *Saccharomyces cerevisiae* reverse gene mutation assay	1993 US production 1.44billion lb; EPA Drinking Water standard: 250,000 ug/L sulfate ion
Zinc Sulfate	Irritating to skin, eyes and mucous membranes; Use as an emetic may result in hemolytic and renal toxicity; Ames negative in TA97, TA102 with and without activation with S-9; Negative in Cell transformation with Syrian hamster embryo cells; Negative in *Saccharomyces cerevisiae.*	Regulated by Clean Water Act; subject to effluent regulations: EPA DW 5000ug/L ; US production $3.5x10^{10}$g (1985)

8. OPP REDs (Reregistration Eligibility Decision Document)

Mineral Acid RED

The following information on the acute toxicity of sulfuric acid was extracted from the 1993 Mineral Acid RED: The oral LD_{50} is 350 mg/kg, toxicity category II. The dermal LD_{50} is > 2000 mg/kg, toxicity category III. Sulfuric acid is toxicity category I for eye and dermal irritation. No other toxicological data were required based on the use patterns at the time of the issuance of the RED and the corrosiveness shown in the acute studies for dermal and eye irritation.

There was also information on the acute toxicity of sodium bisulfate in the 1993 RED: The oral LD_{50} is 3000 mg/kg, toxicity category III. The dermal LD_{50} is > 10,000 mg/kg, toxicity category III. Sodium bisulfate is toxicity category I for eye irritation, and toxicity category IV for dermal irritation. No other toxicological data were required based on the use patterns at the time of the issuance of the RED and the fact that it forms ubiquitous metabolic products, sodium and sulfate, that are of little toxicological concern.

Iron Salts RED

The Iron Salts RED (1993) contains toxicity information on ferric sulfate, ferrous sulfate monohydrate, and ferrous sulfate heptahydrate. The ferric sulfate oral LD_{50} is 1487 to 2101 mg/kg, toxicity category III. The dermal LD_{50} is > 2000 mg/kg, toxicity category III. The inhalation LC_{50} is > 1.1 mg/L, toxicity category III. Ferric sulfate is toxicity category I for eye irritation and toxicity category IV for dermal irritation. For ferrous sulfate heptahydrate the LD_{50} is 1520 mg/kg. A sensitization study with ferric and ferrous sulfate found no indication of contact sensitization by this compound.

According to the RED, a "mutagenicity study in *E. coli* reported positive results at 30 umol/L. With due regard for the continuing exposure that human beings have had to the iron and sulfate components of these chemicals over many generation, it is considered unlikely that this reported result in microorganisms has any bearing on probable effects in humans or other mammals at the levels expected from use of these compounds as pesticides."

Zinc Salts RED

The following information on the acute toxicity of zinc sulfate was extracted from the 1992 Zinc Salts RED: The oral LD_{50} is > 2949 mg/kg, toxicity category III. Zinc sulfate acid is classified as toxicity category I for eye irritation based on one study in which "severe irritation was found when 0.09 g of 99% zinc sulfate was applied to rabbit eyes. In another study, the application of 420 ug zinc sulfate to the rabbit eye found moderate irritation." Zinc sulfate is toxicity category IV for dermal irritation (very slight irritation).

In a chronic study, "zinc sulfate caused hematological changes in rats and dogs fed about

100 ppm in the diet. ... In another report, mice given up to 5000 ppm of zinc as zinc sulfate in drinking water showed no evidence of carcinogenicity and no differences between treated and control groups."

"When rats were given 333 mg/kg zinc sulfate orally on days 1-18 of pregnancy, there was post-implantation mortality. Teratologic studies with oral zinc sulfate in three species of animals were negative for effects on pregnancy, maternal or fetal survival, or abnormalities. In these studies mice were given up to 30 mg/kg/day for days 6-15 of gestation, rats were given up to 42.5 mg/kg/day for days 6-15 of gestation, and hamsters were given up to 88 mg/kg/day for days 6-10 of gestation.

According to the RED, "[p]ositive results have been seen with zinc sulfate in some studies, including a *Drosophila melanogaster* sex chromosome assay with an oral 5 mmol/L dose and a mutation assay with *Saccharomyces cerevisiae* at 100 mmol/L. DNA inhibition was seen in human HeLa cells at 1 umol/L/4 hours and oncogenic transformation occurred at 200 umol/L with hamster embryo."

It was concluded that: "Although some positive mutagenicity studies have been reported, there is no indication of mutagenic effects in normal living organisms from everyday exposure. Living organisms have long been exposed to the components of zinc [sulfate] without such exposure being attributed to mutagenicity."

9. FDA GRAS (Generally Recognized As Safe) Assessments

<u>Ammonium Sulfate</u>

In the FDA Assessment titled "Evaluation of the Health Aspects of Certain Ammonium Salts as Food Ingredients" (1974), the following general conclusion on ammonium compounds was reached:

> "Ammonia and ammonium ion are integral components of normal metabolic processes and play an essential role in the physiology of man. Although there have been no significant feeding studies specifically designed to ascertain the safety threshold of ammonium compounds as food ingredients, numerous metabolic studies have been reported in the scientific literature. Extrapolation of these findings to the concentrations of ammonium compounds normally present in foods does not suggest that there would be untoward effects at such levels."

Ammonium sulfate was evaluated in the "FDA Assessment titled Evaluation of the Health Aspects of Sulfuric Acid and Sulfates as Food Ingredients." (1975) Ammonium sulfate has been used in food in the US since 1957. For infants (0 to 23 months) the average daily intake of ammonium sulfate in 1975 ranged from 0.53 to 2.58 mg/kg. For adults, it was 1.01 mg/kg.

<u>Magnesium Sulfate</u>

The FDA Assessment is titled "Evaluation of the Health Aspects of Magnesium Salts as Food Ingredients" (1976). Magnesium is (1) a dietary essential, (2) involved in many metabolic reactions, (3) important in electrolyte balance, and (4) present in fruits, vegetables, grains, milk, meat and fish. There are no chronic toxicity data. The "status of magnesium as a ubiquitous and essential dietary ingredient for the maintenance of homeostatic and bioenergetic mechanisms leads to the opinion that none of the available evidence suggests any probable hazard when any of the GRAS compounds of magnesium is used as a food ingredient." It was concluded that there was no available information on magnesium sulfate that "demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current and in the manner now practiced, or which might reasonably be expected in the future."

Potassium and Sodium Sulfate

The FDA Assessment is titled "Evaluation of the Health Aspects of Sulfuric Acid and Sulfates as Food Ingredients." (1975). For infants (0 to 23 months) the average daily intake of potassium sulfate in 1975 ranged from 0.05 to 0.49 mg/kg. For adults, it was 0.17 mg/kg. No information was given for sodium sulfate.

Sulfates are present in many foods. Several amino acids contain sulfur. "Sulfates are not rapidly absorbed from the gastrointestinal tract." In a metabolism studies in rats, mice and dogs, it was observed that most sulfate (in rats greater than 80%) was excreted in 24 hours, most of it in the urine.

> "Sulfates are natural constituents of foods and normal products of sulfur metabolism in animals.....it is evident that the toxic manifestations following oral administration of the sulfates considered in this report appear only at levels that are many times greater than those to which man is exposed in his daily diet." It was concluded that: "There is no evidence in the available information on sulfuric acid, and on ammonium, calcium, potassium, and sodium sulfates that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in future."

Zinc Sulfate

In the "GRAS (Generally Recognized As Safe) Food Ingredients - Zinc Salts" document (1972), the available information related to the safety of zinc sulfate as a food ingredient is summarized. However, the document offered no conclusions.

10. FAO/WHO Expert Committee on Food Additives

WHO performed an assessment on sodium sulfate in 2000. This assessment references an evaluation of the sulfate ion at the twenty-ninth meeting (Annex 1, reference 70). At that time an ADI of "not specified" was established based on the fact that "sulfate is a natural constituent of food and is a product of sulfur metabolism in animals." Sodium sulfate was not included in that

ADI: at the time, there was no information to indicate the sodium sulfate was being used as a food-grade material.

Various studies were described including those on renal clearance and laxative trials in humans, and long-term and developmental studies in mice. It was concluded:

> "...that the results of the published studies in experimental animals do not raise concern about the toxicity of sodium sulfate. The compound has a laxative action, which is the basis for its clinical use. The minor adverse effects reported after use of ingested purgative preparations containing sodium sulfate may not be due to the sodium sulfate itself.
>
> In the absence of any evidence of toxicity, the Committee allocated a temporary ADI 'not specified'.....The ADI was made temporary because no information was available on the functional effect and actual uses of sodium sulfate in foods."

11. Human Health Hazard Characterization:

Sulfuric acid in its concentrated form is highly corrosive. Due to this property toxicity testing can only be performed on dilute concentrations or on neutralized forms of the acid such as a salt. The consequences of acute exposure to sulfuric acid are well-understood. "Concentrated sulfuric acid has an extremely irritant, corrosive, and destructive action on all living matter including human tissues, not by virtue of its acidity (in concentrated form it is only slightly ionized) but because of its affinity for water. The affinity is so strong that it will remove the elements of water from even anhydrous organic matter such as carbohydrates, resulting in charring or carbonization with the liberation of heat. In sulfuric acid splashing accidents, the heat liberated by dilution of the concentrated acid with water used to flush the affected areas, can add thermal burn to chemical injury of the body." Thus sulfuric acid "can burn and char the skin. It is even more rapidly injurious to the mucous membranes, and exceedingly dangerous to the eyes. Dilute sulfuric acid, while it does not possess this charring property, irritates the skin and mucous membranes by virtue of its acidity and can cause dermatitis."

Exposure to a mist of sulfuric acid can cause irritant effects on the mucous membranes and chemical corrosive effects upon the teeth. Strong inorganic acid mists containing sulfuric acid are listed as known human carcinogens.

Exposure to sulfuric acid in pesticide products as an inert ingredient would be in the role of a pH adjuster, that is, a liquid form, not a mist. This is indicative of the use of small amounts of sulfuric acid that are incorporated in a pesticide product to lower the pH . After the pH adjustment is performed, the sulfuric acid would be neutralized. As an active ingredient sulfuric acid is subject to FIFRA registration requirements and various labeling language as specified in the RED (Reregistration Eligibility Decision). Sulfuric acid must be used and applied according to good manufacturing or good agricultural practices. However, there are no significant adverse effects, to the general public or any population subgroup from consumption of residues of sulfuric acid resulting from such uses.

As a group these salts of sulfuric acid constitute a group of chemicals with many uses including direct use in the food supply. The available toxicity data indicates that the human body metabolizes sulfate, ammonium, calcium, iron, magnesium, potassium, sodium and zinc ions through well-understood pathways. In fact, all are necessary human nutrients. Various salts of sulfuric acid have been used in the food supply for a number of years. There are no available data to indicate any significant adverse effects to the general public or any population subgroup from consumption of residues of the ammonium, calcium, iron, magnesium, potassium, sodium, and zinc salts of sulfuric acid resulting from pesticide product uses.

Given the long history of safe use, the available toxicity data, an understanding of the human body's ability to metabolize these chemicals, and the evaluations by FDA and WHO, the IIFG believes that ammonium, sodium, potassium, magnesium, calcium, iron, and zinc sulfate salts are of low oral toxicity.

12. Type of Risk Assessment/Risk Characterization:

The toxicity of these chemicals derives from the irritation and caustic effects; therefore, a qualitative assessment for all pathways of human exposure (food, drinking water, and residential) is appropriate.

Given the widespread occurrence of sulfuric acid and its salts in the existing food supply, the amounts that can be applied to food as a result of a use in a pesticide product would not be expected to significantly increase the existing amounts in the food supply. There is no available information on any of the salts of sulfuric acid considered in this document indicative of a human health hazard resulting from the EPA-regulated uses as well as the FDA GRAS uses to the general public or any population subgroup. No additional information is needed to assess their safety.

13. Sensitivity of Infants and Children:

Due to its acidic nature, its corrosive potential, there is high acute toxicity for sulfuric acid. Sulfuric acid must be used in pesticide products according to good manufacturing or good agricultural practices. The ammonium, sodium, potassium, magnesium, calcium, iron, and zinc salts of sulfuric acid have low toxic potential. At this time, there is no concern for potential sensitivity to infants and children. A safety factor analysis has not been used to assess the risk. For the same reasons the additional tenfold safety factor is unnecessary.

14. Environmental Fate and Ecotoxicity Assessment/Characterization:

In general, the constituents of the mineral acids, such as sulfuric acid, are commonly found in soil and water in the environment suggesting that releasing low levels of these chemicals would not normally be expected to adversely effect wildlife or water resources. Large releases may adversely affect wildlife and water resources either directly or indirectly. Direct effects may result from exceeding toxicity thresholds of specific chemicals. Indirect effects may be manifested through disrupting ecosystems through altering pH or increasing availability of algal nutrients.

Sulfuric acid is a strong acid. The magnitude of the pH changes, and thus the magnitude of effects, would depend on a number of factors including the amount of material released and the buffering capacity of the exposed soil or water. Normal aquatic pHs range from 5 to 9. EPA's Office of Water recommended water quality criteria for pH are 6.5 to 9 for freshwater and 6.5 to 8.5 for saltwater. At higher or lower pH aquatic life is expected to be adversely impacted. In addition, rapid changes in pH can also be detrimental to aquatic life. Sulfuric acid is not expected to be persistent in the environment. Instead it is expected to dissociate, react with organic or inorganic materials, and complex with ionic substrates.

The magnesium, sodium, potassium, iron, and zinc salts of sulfuric acid should dissociate in water resulting in a positively charged (cation) metal in solution. Dissociation is frequently dependent on pH, with lower (more acidic) pHs resulting in higher levels of dissociation and greater solubility. Aquatic toxicity of metals varies with the species of metal and its concentration. EPA's freshwater water quality criteria for iron is 1 ppm implying relatively low toxicity. Zinc has recommended criteria implying these metals are more toxic. Metals do not degrade and thus are permanent in the environment. They are likely to dissipate by being sequestered in soil, sediment, and plants.

15. Cumulative Exposure:

Section 408(b)(2)(D)(v) requires that, when considering whether to establish, modify, or revoke a tolerance, the Agency consider "available information" concerning the cumulative effects of a particular pesticide chemical's residues and "other substances that have a common mechanism of toxicity." The chemicals considered in this document are structurally related; however, all of the salts are low toxicity chemicals. Therefore, the resultant risks separately and/or combined should also be low. EPA does not have, at this time, available data to determine whether these pesticide chemicals have a common mechanism of toxicity with other substances or how to include these pesticide chemicals in a cumulative risk assessment.

16. Determination of Safety:

Based on its review and evaluation of the available information, EPA concludes that there is a reasonable certainty that no harm will result to the general population, and to infants and children from aggregate exposure to residues of sulfuric acid and its ammonium, sodium, potassium, calcium, magnesium, iron, and zinc salts. Therefore, the following exemptions from the requirement of a tolerance are reassessed: In 40 CFR 180.2 ferrous sulfate. In 40 CFR 180.1001 (c) ammonium sulfate, ferric sulfate, magnesium sulfate, potassium sulfate, sodium sulfate, sulfuric acid, zinc sulfate (basic and monohydrate), and zinc sulfate (basic and monohydrate). In 40 CFR 180.1001 (d) sodium bisulfate. In 40 CFR 180.1001 (e) sodium sulfate and zinc sulfate (basic and monohydrate). Also sulfuric acid in 40 CFR 180.1019.

17. List Reclassifications:

The following List reclassifications are made or confirmed:

Sulfuric acid: List 4B. With the restriction of use as a pH control agent; current limitation remains in place
Ammonium sulfate: List 4B
Ferrous sulfate: List 4B
Ferric sulfate: List 4B
Magnesium sulfate: List 4A, given its neutral pH in solution
Potassium sulfate: List 4A, given its neutral pH in solution
Sodium sulfate: List 4A, given its neutral pH in solution
Sodium bisulfate: List 4B, given its acidic nature, similar to that of sulfuric acid
Zinc sulfate: List 4B

The following table lists the various chemical names, CAS Reg. No., and CAS Index Names that will be used for listing in 40 CFR.180. Note that both the anhydrous and the hydrated forms are included. The Agency sees no reason to distinguish between these chemicals given that the only difference is the attachment of the water molecules.

Chemical Name	CAS. Reg. No.	Chemical Abstacts Index Name
Sulfuric acid	7664-93-9	Sulfuric acid (8CI, 9CI)
Ammonium sulfate	7783-20-2	Sulfuric acid diammonium salt (8CI, 9CI)
Ammonium bisulfate	7803-63-6	Sulfuric acid, monoammonium salt (8CI, 9CI)
Calcium sulfate	7778-18-9	Sulfuric acid, calcium salt (1:1) (8CI, 9CI)
Calcium sulfate ½ hydrate {CaSO4 . 1/2H20}	10034-76-1	Sulfuric acid, calcium salt, hydrate (2:2:1) (9CI)
Calcium sulfate dihydrate {CaSO4 . 2H20}	10101-41-4	Sulfuric acid, calcium salt (1:1), dihydrate (8CI, 9CI)
Ferric sulfate	10028-22-5	Sulfuric acid, iron(3+) salt (3:2) (8CI, 9CI)
Iron(II) sulfate	7720-78-7	Sulfuric acid, iron(2+) salt (1:1) (8CI, 9CI)

Chemical Name	CAS. Reg. No.	Chemical Abstacts Index Name
Iron(II) sulfate dihydrate	10028-21-4	Sulfuric acid, iron(2+) salt (1:1), dihydrate (9CI)
Iron (II) sulfate heptahydrate {FeSO4 . 7H20}	7782-63-0	Sulfuric acid, iron(2+) salt (1:1), heptahydrate (8CI, 9CI)
Iron (II) sulfate pentahydrate {FeSO4 . 5H20}	13450-80-1	Sulfuric acid, iron(2+) salt (1:1), pentahydrate (8CI, 9CI)
Iron (II) sulfate tetrahydrate {FeSO4 . 4H20}	20908-72-9	Sulfuric acid, iron(2+) salt (1:1), tetrahydrate (8CI, 9CI)
Iron (II) sulfate ennahydrate {FeSO4 . 9H20}	73248-92-7	Sulfuric acid, iron(2+) salt (1:1), nonahydrate (9CI)
Magnesium sulfate	7487-88-9	Sulfuric acid magnesium salt (1:1) (8CI, 9CI)
Magnesium sulfate heptahydrate (epsom salt) {MgSO4 . 7H2O}	10034-99-8	Sulfuric acid magnesium salt (1:1), heptahydrate (8CI, 9CI)
Magnesium sulfate monohydrate {MgSO4 . H2O}	14168-73-1	Sulfuric acid magnesium salt (1:1), monohydrate (8CI, 9CI)
Potassium pyrosulfate {K2S2O7}	7790-62-7	Disulfuric acid, dipotassium salt (9CI)
Potassium hydrogen sulfate {KHSO4}	7646-93-7	Sulfuric acid, monopotassium salt (8CI, 9CI)
Potassium sulfate	7778-80-5	Sulfuric acid dipotassium salt (8CI, 9CI)
Sodium sulfate	7757-82-6	Sulfuric acid disodium salt (8CI, 9CI)
Sodium sulfate decahydrate {Na2SO4 .10H2O}	7727-73-3	Sulfuric acid disodium salt, decahydrate (8CI, 9CI)
Sodium sulfate heptahydrate {Na2SO4 .7H2O}	13472-39-4	Sulfuric acid disodium salt, heptahydrate (8CI, 9CI)
Sodium pyrosulfate {Na2S2O7}	13870-29-6	Disulfuric acid, disodium salt (9CI)
Sodium sulfate hydrogen monohydrate {NaHSO4 .H2O}	10034-88-5	Sulfuric acid, monosodium salt, monohydrate (8CI, 9CI)
Sodium bisulfate	7681-38-1	Sulfuric acid, monosodium salt (8CI, 9CI)
Zinc sulfate (basic and monohydrate)	68813-94-5	Sulfuric acid, zinc salt, basic (9CI)

Chemical Name	CAS. Reg. No.	Chemical Abstacts Index Name
	7446-19-7	Sulfuric acid, zinc salt (1:1), monohydrate (8CI, 9CI)
Zinc sulfate	7733-02-0	Sulfuric acid, zinc salt (1:1) (8CI, 9CI)
Zinc sulfate heptahydrate {ZnSO4 . 7H2O}	7446-20-0	Sulfuric acid, zinc salt (1:1), heptahydrate (8CI, 9CI)
Zinc sulfate hexahydrate	13986-24-8	Sulfuric acid, zinc salt (1:1), hexahydrate (8CI, 9CI)

Attachment:

EFED Review of Mineral Acids (Birchfield; May 7, 2002)